Effect of Zidovudine Regimens on CD4 Count over Time

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INTRO

Acquired immunodeficiency syndrome, AIDS, is a widespread virus that is highly prevalent in today's society. Understanding its effects is extremely important for public health officials in regards to planning resources towards prevention research, disease control, and public assistance. While no cure exists, many treatments are being tested in an attempt to slow the disease's progress or nullify its effects.

The experiment was a randomized, double-blind study of AIDS patients with advanced immune suppression, that corresponds to CD4 counts of less than or equal to 50 cells/mm^3.

1309 patients were randomized to be administered four different daily treatments of medication called Zidovudine. The four treatments are as follows:

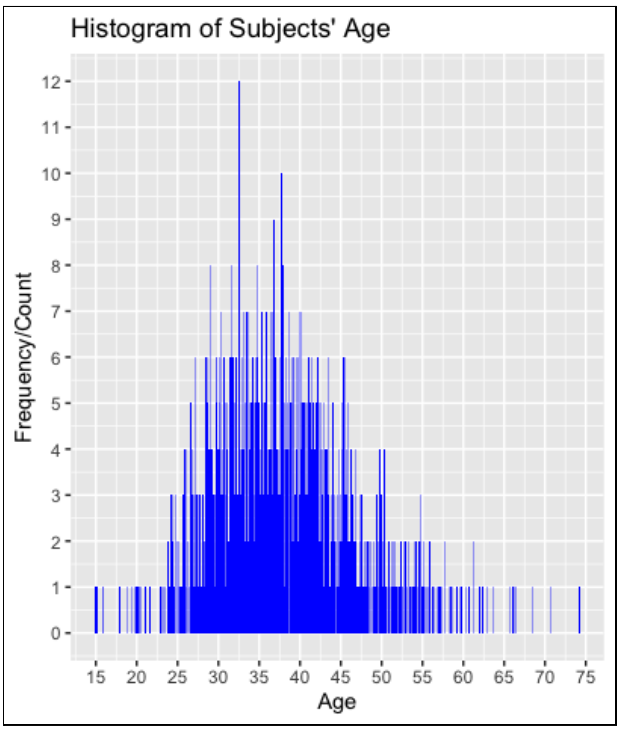
Treatment 1: zidovudine alternating monthly with 400mg didanosine
Treatment 2: zidovudine plus 2.25mg of zalcitabine
Treatment 3: zidovudine plus 400mg of didanosine
Treatment 4: zidovudine plus 400mg of didanosine plus 400mg of nevirapine

The variables of interest are listed below:
log_CD4: log transformed CD4 counts (log(CD4 + 1))
Week: time since baseline (weeks)
Age: age of subject (years)
Gender: male and female

Our goal is to compare the effect of treatment types on the changes in both log transformed CD4 and CD4 counts over time.

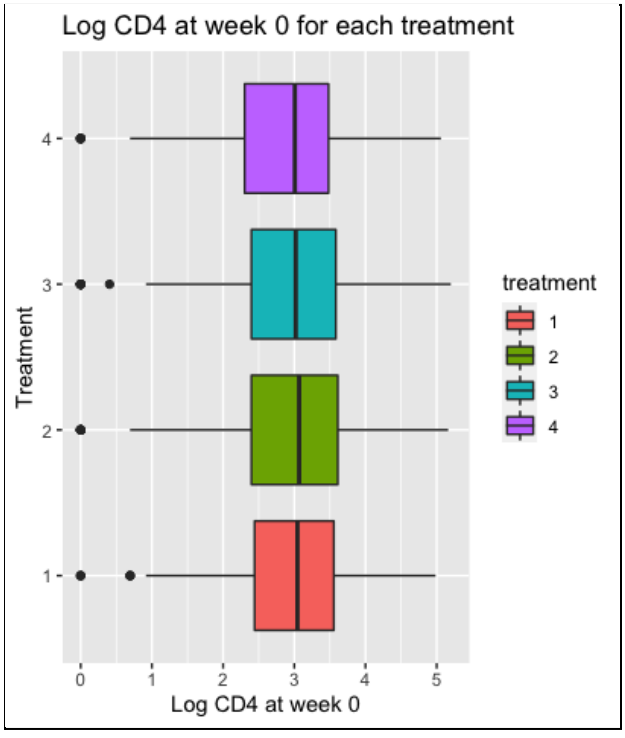
EXPLORATORY DATA ANALYSIS

Univariate Summary (Numerical/Graphical)

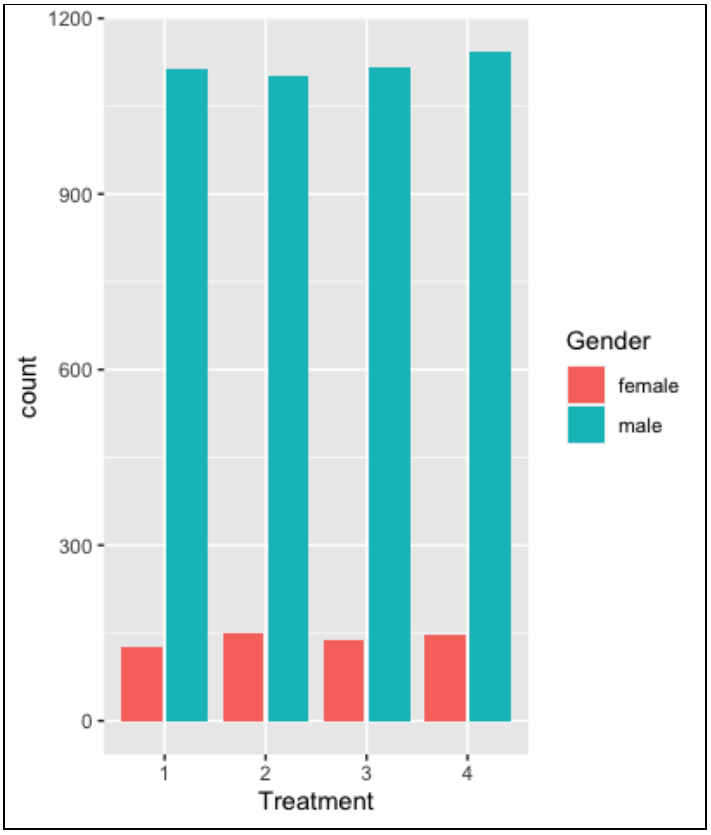


Patients' ages range anywhere from 15 to 75 years old. However, 95% of the data is concentrated on patients between 25 and 55 years old. The patients' ages seem to follow a normal distribution.

Given that the patients in this trial were **randomized** to one of four different treatments, we should expect to see very similar boxplots for the log(CD4) count at week zero. We are unable to plot log(CD4) at different week times as measurement times are inconsistent and not uniform.

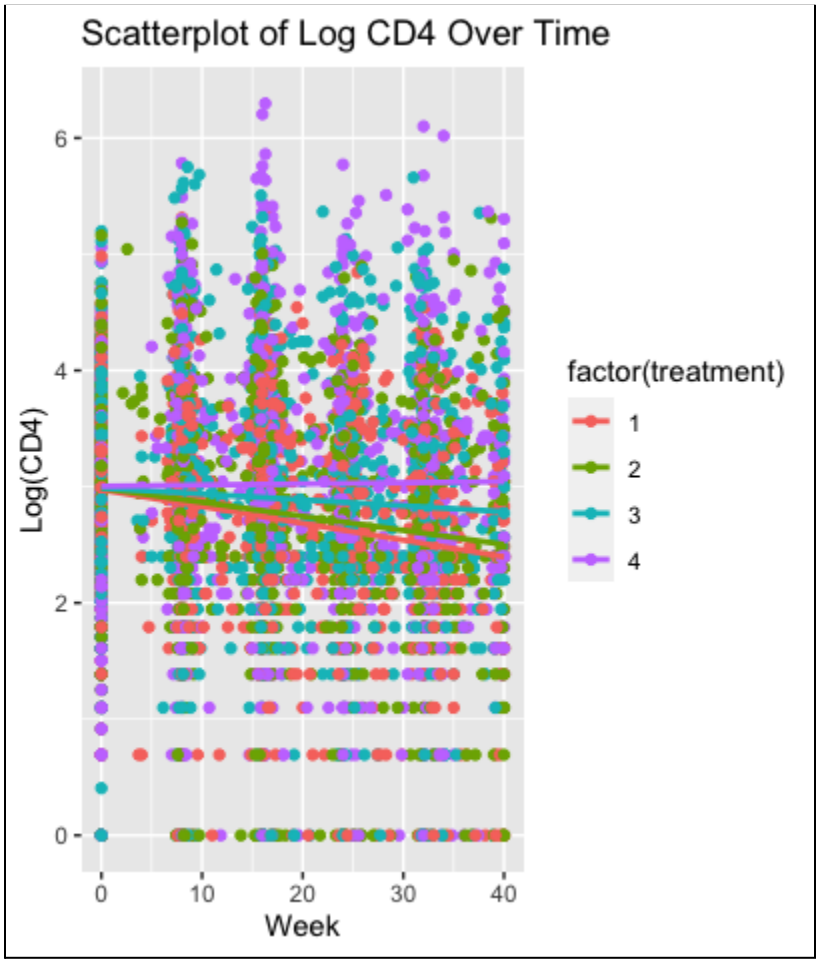


We notice that the proportion of male to females is about the same across all 4 treatments, however, because the overall number of males is so much larger than those of females, the variable “gender” could possibly not be statistically significant in our models. We will later test this.

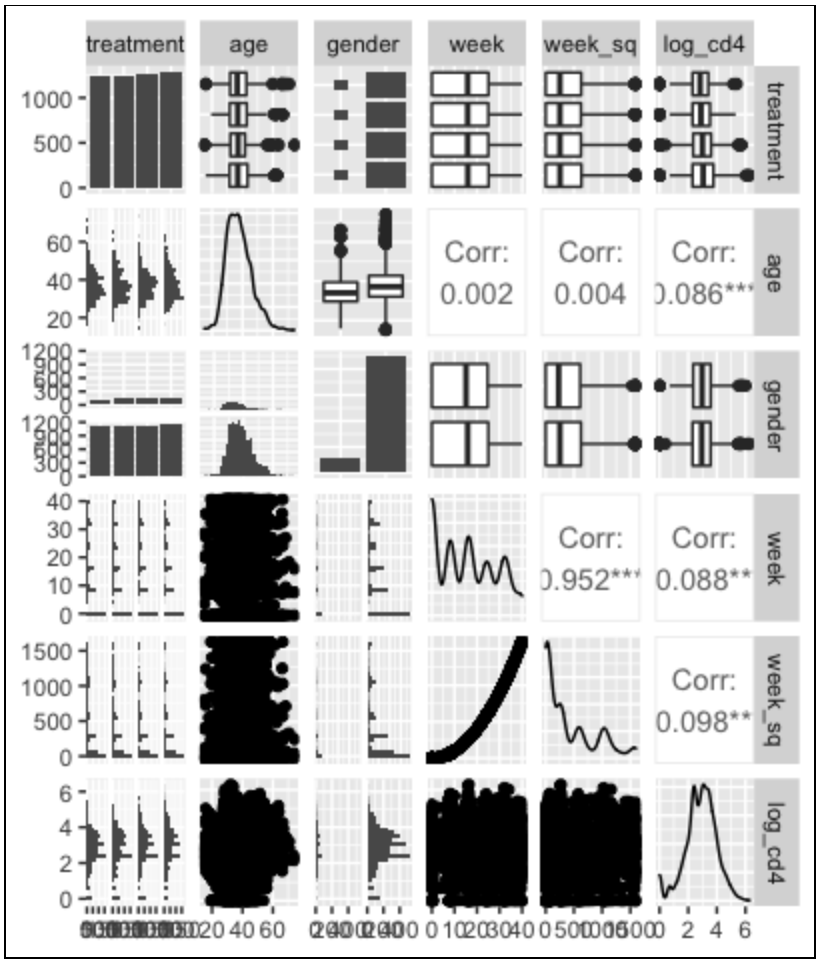


Bivariate Summary (Numerical/Graphical)

During the exploratory process, it is good to visualize how the response variable (in this case the log(CD4) changes over time for different levels of treatments. We used a smoothing method to plot the mean of log(CD4) over time.



As we can see, although the data is well-scattered throughout the 40-week study, there seem to be different effects among the treatments. Treatments 1, 2, and 3 seem to have negative relationships with log(CD4) over time. Additionally, we note that the mean for treatments 1, 2, and 3 are lower at the end of the 40-week period compared to week 0. We will later test these ideas once the model has been created.



Given the plots above, it is hard to say that gender and age will be good predictors of a patient's CD4 count because there is no strong evident trend in the data. However, output summaries in addition to statistical tests of the model will be a better indicator of the significance of the variable than the graphs above.

Imbalances/Outliers

It is important to note that not all patients have the same number of measurements. Number of measurements per subject ranged from 1 to 8. Additionally, measurement times are not uniform—i.e. The subjects were not all recorded at the same time or at the same intervals.

No outliers were found in the dataset. We will review this during our residual analysis with Mahalanobis Distance.

MODEL BUILDING

We begin with a full linear mixed effects model of:

$$Log(CD4) \sim Age + Gender + Week + AgeTrt + GenderTrt + WeekTrt + b_0$$

(Note that we do not include the main effect of treatment as the experiment is randomized)

The summary output is listed and states that a majority of our covariates are significant. However, the main effects of age and gender may not be significant. Following the output, we will test their significance.

```
Linear mixed-effects model fit by maximum likelihood
  Data: aids
       AIC      BIC   logLik
  12179.98 12277.85 -6074.99

Random effects:
 Formula: ~1 | id
        (Intercept)  Residual
StdDev:   0.8607348 0.6189748

Fixed effects:  log_cd4 ~ age + gender + week + age:treatment + gender:treatment +      week:treatment
                           Value  Std.Error   DF    t-value p-value
(Intercept)            2.6469689 0.13452961 3723  19.675734  0.0000
age                    0.0032706 0.00439097 1300   0.744848  0.4565
gendermale             0.2405657 0.15373339 1300   1.564824  0.1179
week                  -0.0163963 0.00148935 3723 -11.009049  0.0000
age:treatment2         0.0122064 0.00511963 1300   2.384228  0.0173
age:treatment3         0.0074441 0.00496402 1300   1.499613  0.1340
age:treatment4         0.0132074 0.00498103 1300   2.651550  0.0081
gendermale:treatment2 -0.4872267 0.20968015 1300  -2.323666  0.0203
gendermale:treatment3 -0.3080930 0.20286136 1300  -1.518737  0.1291
gendermale:treatment4 -0.5544853 0.20435319 1300  -2.713368  0.0067
week:treatment2        0.0020909 0.00209107 3723   0.999931  0.3174
week:treatment3        0.0072320 0.00209889 3723   3.445631  0.0006
week:treatment4        0.0152579 0.00206701 3723   7.381631  0.0000
 Correlation:
                      (Intr) age    gndrml week   ag:tr2 ag:tr3 ag:tr4 gndr:2 gndr:3 gndr:4 wk:tr2 wk:tr3
age                   -0.561
gendermale            -0.258 -0.590
week                  -0.043 -0.052 -0.040
age:treatment2        -0.064 -0.551  0.647  0.068
age:treatment3        -0.040 -0.583  0.661  0.069  0.522
age:treatment4        -0.028 -0.588  0.655  0.068  0.520  0.535
gendermale:treatment2  0.062  0.504 -0.700  0.035 -0.918 -0.479 -0.477
gendermale:treatment3  0.030  0.540 -0.715  0.038 -0.480 -0.913 -0.492  0.520
gendermale:treatment4  0.026  0.539 -0.709  0.037 -0.476 -0.490 -0.915  0.516  0.533
week:treatment2        0.003  0.052  0.036 -0.711 -0.102 -0.048 -0.048 -0.044 -0.028 -0.027
week:treatment3        0.011  0.048  0.033 -0.709 -0.047 -0.098 -0.048 -0.026 -0.054 -0.027  0.504
week:treatment4        0.009  0.050  0.034 -0.720 -0.048 -0.049 -0.102 -0.026 -0.028 -0.048  0.512  0.510

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-4.21488756 -0.44964434  0.03257531  0.52259661  3.74765834

Number of Observations: 5036
Number of Groups: 1309
```

All of the following models are linear mixed models, with a random effect on slope. We compare the linear "full" model with the three "reduced" models that exclude the main effect of age, gender individually, in addition to excluding the main effects of age and gender together.

We compare them using an "ML" method and a combination of Akaike's Information Criterion and Likelihood Ratio Test, when appropriate.

model_linear	$Log(CD4) \sim Age + Gender + Week + AgeTrt + GenderTrt + WeekTrt$
model_at	$Log(CD4) \sim Gender + Week + AgeTrt + GenderTrt + WeekTrt$
model_gt	$Log(CD4) \sim Age + Week + AgeTrt + GenderTrt + WeekTrt$
model_w	$Log(CD4) \sim Week + AgeTrt + GenderTrt + WeekTrt$

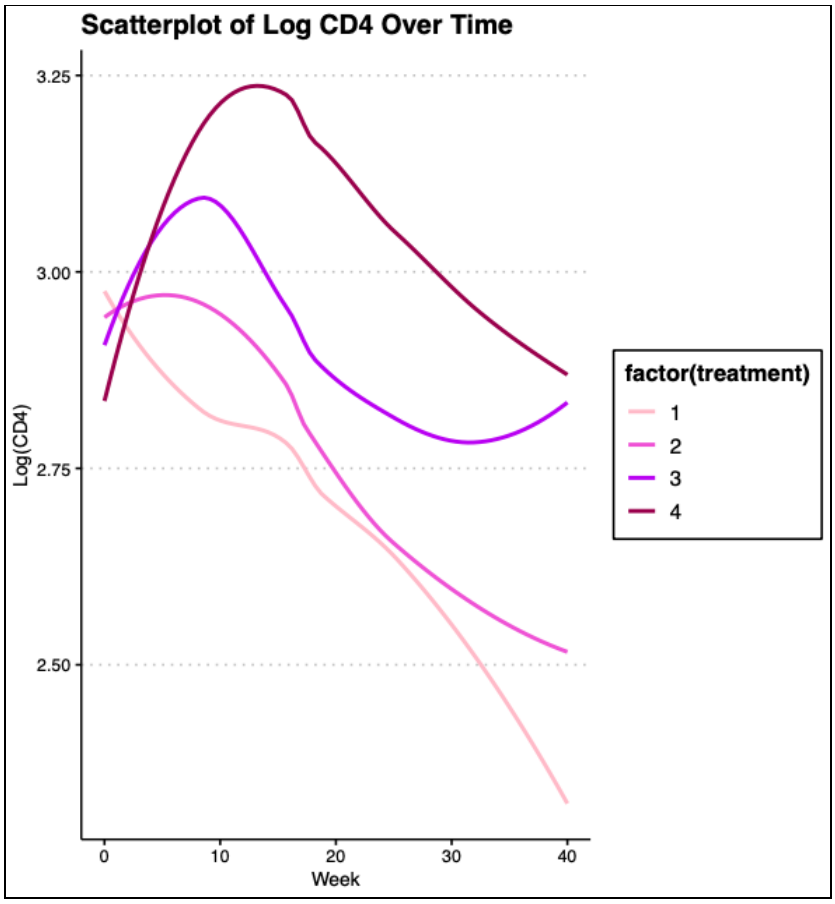
An ANOVA test comparing the models is listed below:

	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
model_linear	1	15	12179.98	12277.84	-6074.990			
model_at	2	18	12181.11	12298.55	-6072.557	1 vs 2	4.866623	0.1818
model_gt	3	15	12179.98	12277.84	-6074.990	2 vs 3	4.866623	0.1818
model_w	4	15	12179.98	12277.84	-6074.990			

Interestingly, the AIC and log-likelihood tests seem to contradict each other in their conclusions. AIC judges that model_linear, model_gt, and model_w are the same and are better than model_at while the LRT deems model_at the best. For continuity and simplicity, we will continue with the full model as we continue to add more covariates. We will also revisit the significance of age as a main effect.

Nonlinear Relationship of Log(CD4) over Time

The smoothed graph of log(CD4) over time suggests that a piecewise or quadratic model may be preferred over a linear model. The different models are as follows:



Piecewise:

$$Y \sim Age + Gender + Week + (Week - 10) + AgeTrt + GenderTrt + WeekTrt$$

Piecewise (with interaction):

$$Y \sim Age + Gender + Week + (Week - 10) + AgeTrt + GenderTrt + WeekTrt + (Week - 10)Trt$$

Quadratic:

$$Y \sim Age + Gender + Week + Week^2 + AgeTrt + GenderTrt + WeekTrt$$

Quadratic (with interaction):

$$Y \sim Age + Gender + Week + Week^2 + AgeTrt + GenderTrt + WeekTrt + Week^2Trt$$

An ANOVA test on these different models gives the output:

	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
model_linear	1	15	12179.98	12277.84	-6074.990			
model_piecewise	2	16	12134.40	12238.79	-6051.198	1 vs 2	47.58283	<.0001
model_piecewise2	3	19	12116.07	12240.03	-6039.033	2 vs 3	24.33159	<.0001
model_quad	4	16	12135.83	12240.22	-6051.914	3 vs 4	25.76301	<.0001
model_quad2	5	19	12112.99	12236.95	-6037.496	4 vs 5	28.83591	<.0001

As the full model is nested within the piecewise and quadratic models, we can compare using log-likelihood. The comparison of all the models' log-likelihoods dictates that the piecewise (with interaction) and quadratic (with interaction) are the best two models.

$$logLik_{piecewise2} > logLik_{piecewise2} > logLik_{linear}$$
$$logLik_{quad2} > logLik_{quad} > logLik_{linear}$$

Since the quadratic or piecewise are not nested within the other, we can compare them using Akaike's Information Criterion, or AIC. As $AIC_{quad2} < AIC_{piecewise2}$, we conclude that model_quad2 is the better of the two.

Random Effects

Now we consider different random effects. For the sake of processing power and model simplicity, we will only consider 2 random effects per model: intercept and a main effect. The different models are as follows:

model_quad_a	$Y_{ij} = \beta_0 + \beta_1 Age_i + \ldots + \beta_{16} Week_i^2 Trt_i + b_{0i} + b_{1i} Age_i + \varepsilon_i$
model_quad_g	$Y_{ij} = \beta_0 + \beta_1 Age_i + \ldots + \beta_{16} Week_i^2 Trt_i + b_{0i} + b_{1i} Gender_i + \varepsilon_i$
model_quad_2	$Y_{ij} = \beta_0 + \beta_1 Age_i + \ldots + \beta_{16} Week_i^2 Trt_i + b_{0i} + b_{1i} Week_i + \varepsilon_i$
model_quad_w2	$Y_{ij} = \beta_0 + \beta_1 Age_i + \ldots + \beta_{16} Week_i^2 Trt_i + b_{0i} + b_{1i} Week_i^2 + \varepsilon_i$

An ANOVA test comparing the models gives the output:

	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
model_quad2	1	19	12112.99	12236.95	-6037.496			
model_quad_a	2	21	12116.99	12254.00	-6037.496	1 vs 2	3.385518e-06	1
model_quad_g	3	21	12116.14	12253.15	-6037.070			
model_quad_w	4	21	11972.91	12109.92	-5965.456			
model_quad_w2	5	21	12038.04	12175.05	-5998.020			

Using AIC, we conclude that model_quad_w, the model with a random effect on the intercept and week, is our preferred model.

$$AIC_{week} < AIC_{week2} < AIC_{quad2} < AIC_{gender} < AIC_{age}$$

Chosen Model

Our chosen model is as follows:

$$Y_{ij} = \beta_0 + \beta_1 Age_i + \beta_2 Gender_i + \beta_3 Week_i + \beta_4 Week_i^2 + \beta_5 Age_i I(Trt_i = 2) + \beta_6 Age_i I(Trt_i = 3)$$

$$+ \beta_7 Age_i I(Trt_i = 4) + \beta_8 Gender_i (Trt_i = 2) + \beta_9 Gender_i (Trt_i = 3) + \beta_{10} Gender_i (Trt_i = 4)$$
$$+ \beta_{11} Week_i (Trt_i = 2) + \beta_{12} Week_i (Trt_i = 3) + \beta_{13} Week_i (Trt_i = 4)$$
$$+ \beta_{14} Week_i^2 (Trt_i = 2) + \beta_{15} Week_i^2 (Trt_i = 3) + \beta_{16} Week_i^2 (Trt_i = 4)$$

```
Linear mixed-effects model fit by maximum likelihood
  Data: aids
       AIC      BIC    logLik
  11972.91 12109.92 -5965.456

Random effects:
 Formula: ~1 + week | id
 Structure: General positive-definite, Log-Cholesky parametrization
            StdDev     Corr
(Intercept) 0.79732503 (Intr)
week        0.01616463 0.18
Residual    0.57291889

Fixed effects:  log_cd4 ~ age + gender + week + week_sq + age:treatment +
 gender:treatment +      week:treatment + week_sq:treatment
                              Value  Std.Error   DF   t-value p-value
(Intercept)                2.5870575 0.13070790 3719 19.792664  0.0000
age                        0.0035263 0.00426237 1300  0.827311  0.4082
gendermale                 0.2813344 0.14935445 1300  1.883669  0.0598
week                      -0.0129637 0.00460255 3719 -2.816634  0.0049
week_sq                   -0.0001160 0.00012806 3719 -0.905548  0.3652
age:treatment2             0.0122895 0.00497231 1300  2.471589  0.0136
age:treatment3             0.0067780 0.00480933 1300  1.409345  0.1590
age:treatment4             0.0105521 0.00483930 1300  2.180493  0.0294
gendermale:treatment2     -0.5115665 0.20377835 1300 -2.510406  0.0122
gendermale:treatment3     -0.3274957 0.19667274 1300 -1.665181  0.0961
gendermale:treatment4     -0.5641849 0.19859419 1300 -2.840893  0.0046
week:treatment2            0.0066045 0.00645272 3719  1.023527  0.3061
week:treatment3            0.0199835 0.00646825 3719  3.089472  0.0020
week:treatment4            0.0464606 0.00639605 3719  7.263959  0.0000
week_sq:treatment2        -0.0001275 0.00017819 3719 -0.715576  0.4743
week_sq:treatment3        -0.0004055 0.00018026 3719 -2.249517  0.0245
week_sq:treatment4        -0.0008991 0.00017681 3719 -5.084894  0.0000
```

$$Y_{ij} = 2.587 + 0.004 Age_i + 0.281 Gender_i - 0.013 Week_i - 0.0001 Week_i^2 + 0.012 Age_i I(Trt_i = 2)$$
$$+ 0.007 Age_i I(Trt_i = 3) + 0.011 Age_i I(Trt_i = 4) - 0.512 Gender_i I(Trt_i = 2)$$
$$- 0.327 Gender_i I(Trt_i = 3) - 0.564 Gender_i I(Trt_i = 4) + 0.007 Week_i I(Trt_i = 2)$$
$$+ 0.020 Week_i I(Trt_i = 3) + 0.046 Week_i I(Trt_i = 4) - 0.0001 Week_i^2 I(Trt_i = 2)$$
$$- 0.0004 Week_i^2 I(Trt_i = 3) - 0.0009 Week_i^2 I(Trt_i = 4) + b_{0i} + b_{1i}$$

Revisiting age as a main effect, we find that the two models have the same AIC and log-likelihood. As neither model has less degrees of freedom, they explain the same amount of variation. We will continue with model_quad2 for continuity.

	Model	df	AIC	BIC	logLik
model_quad2	1	19	12112.99	12236.95	-6037.496
model_quad2_no_age	2	19	12112.99	12236.95	-6037.496

Predictions/Comparisons of LME Model

The model predicts that:

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 2 (Zidovudine plus 2.25mg of Zalcitabine), we expect a change in log(CD4) of $\beta_5 Age_i + \beta_8 Gender_i + \beta_{11} Week_i + \beta_{14} Week_i^2$. For a 35-year old male at week 10, we'd expect a change in log(CD4) of -0.032 (or a change of -0.031 in the count of CD4), or in other words, a decrease in the count of CD4.

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 3 (Zidovudine plus 400mg of Didanosine), we expect a change in log(CD4) of $\beta_6 Age_i + \beta_9 Gender_i + \beta_{12} Week_i + \beta_{15} Week_i^2$. For a 35-year old male at week 10, we'd expect a change in log(CD4) of 0.078 (or a change of 0.08 in the count of CD4), or in other words, an increase in the count of CD4.

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 4 (Zidovudine plus 2.400mg of Didanosine plus 400mg of Nevirapine), we expect a change in log(CD4) of $\beta_7 Age_i + \beta_{10} Gender_i + \beta_{13} Week_i + \beta_{16} Week_i^2$. For a 35-year old male at week 10, we'd expect a change in log(CD4) of 0.191 (or a change of 0.21 in the count of CD4), or in other words, an increase in the count of CD4.

We can also compare our model with the log(CD4) values as observed. We will choose subjects with IDs 469 and 1172.

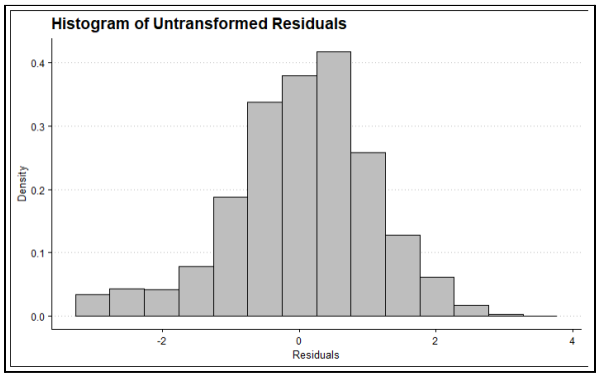
ID	**Week**	**Fitted**	**Observed**	**Fitted - Observed**
469 (Trt = 1, 43.47 y.o male)	0	3.5847	2.8622	0.7225
	8.42	3.5232	4.6250	-1.1018
	24.43	3.3610	3.3322	0.0288
	32.29	3.2596	3.1780	0.0816
1172 (Trt = 4, 23.01 y.o. male)	0	3.2125	2.0794	1.1331

	8.14	3.5574	4.2767	-0.7193
	17	3.7797	4.2627	-0.483
	33.43	3.7705	3.9318	-0.1613

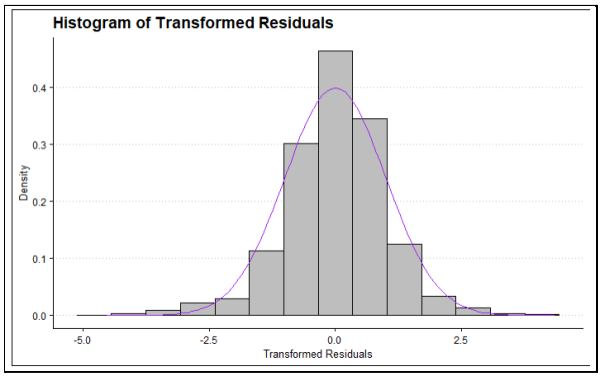
RESIDUAL ANALYSIS

We begin with the standardization of our residuals using Cholesky's decomposition.

Histogram of Untransformed Residuals



Histogram of Transformed Residuals



Visually, we can see that the transformed residuals follow an approximately normal distribution.

QQ Plot

We use the QQ Plot to analyze the normality assumption and visually identify outliers. Below is the output:

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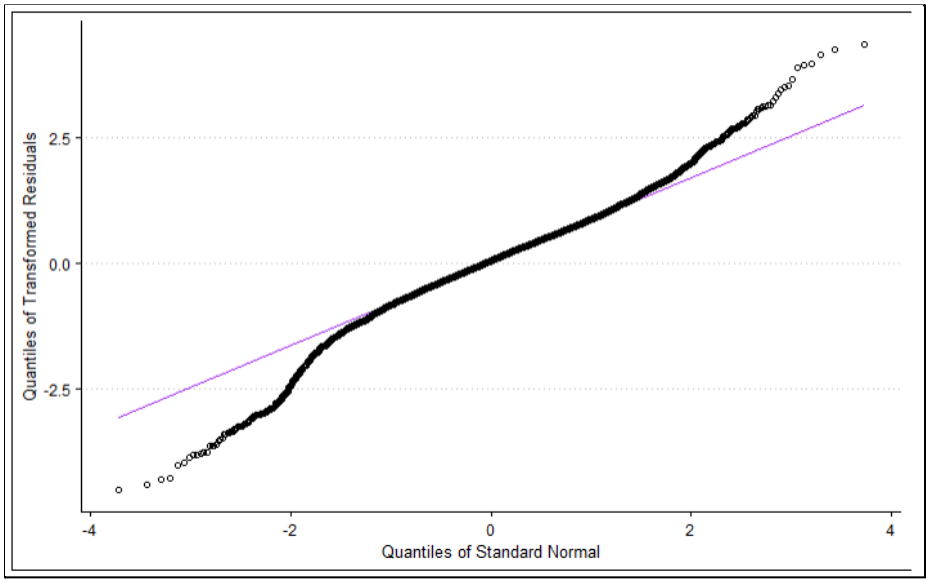


We can see that the tails depart from the straight line, thus the assumption of normality is not met. Possible justifications of this departure are: large expected residuals at baseline because of variability between individuals, and that we can expect large residuals due to this being a random experiment. Despite these ideas, we must look at the other residual graphs to make a definite conclusion.

Mahalanobis Distance

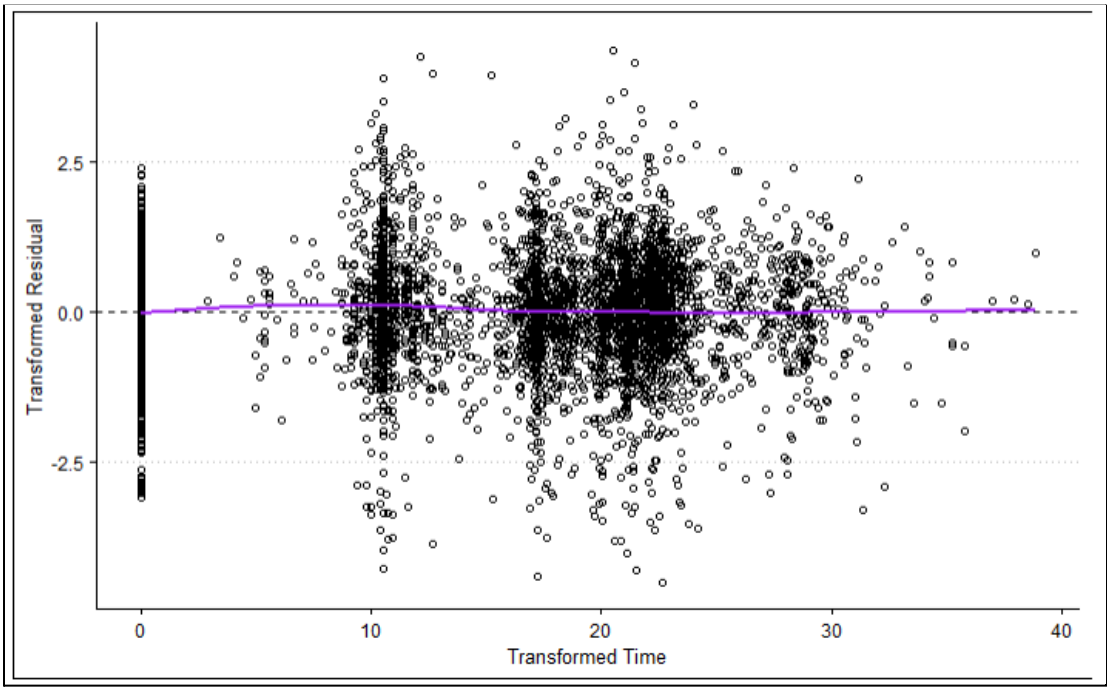
We identify outlying individuals based on their Mahalanobis Distance in which the outliers will have small associated p-values under significance level (α) = 0.05. We expect to have 252 outliers (expected outliers = α * number of observations).

```
# A tibble: 133 x 5
# Groups:   id [133]
      id data                 df     d     p_value
   <dbl> <list>            <dbl> <dbl>       <dbl>
 1   178 <tibble [5 x 1]>      5  39.7 0.000000174
 2   692 <tibble [5 x 1]>      5  35.2 0.000001136
 3  1118 <tibble [5 x 1]>      5  33.4 0.000003310
 4  1207 <tibble [5 x 1]>      5  31.1 0.000008896
 5  1193 <tibble [4 x 1]>      4  28.1 0.0000117
 6   371 <tibble [2 x 1]>      2  20.4 0.0000377
 7   877 <tibble [6 x 1]>      6  29.8 0.0000435
 8  1100 <tibble [3 x 1]>      3  21.8 0.0000717
 9   626 <tibble [5 x 1]>      5  26.2 0.0000806
10  1117 <tibble [5 x 1]>      5  26.1 0.0000858
# ... with 123 more rows
```

By the table row count we can see that we have 133 outliers, which is less than the number expected. We can attribute these outliers to random chance.

Residuals ~ Predicted Time

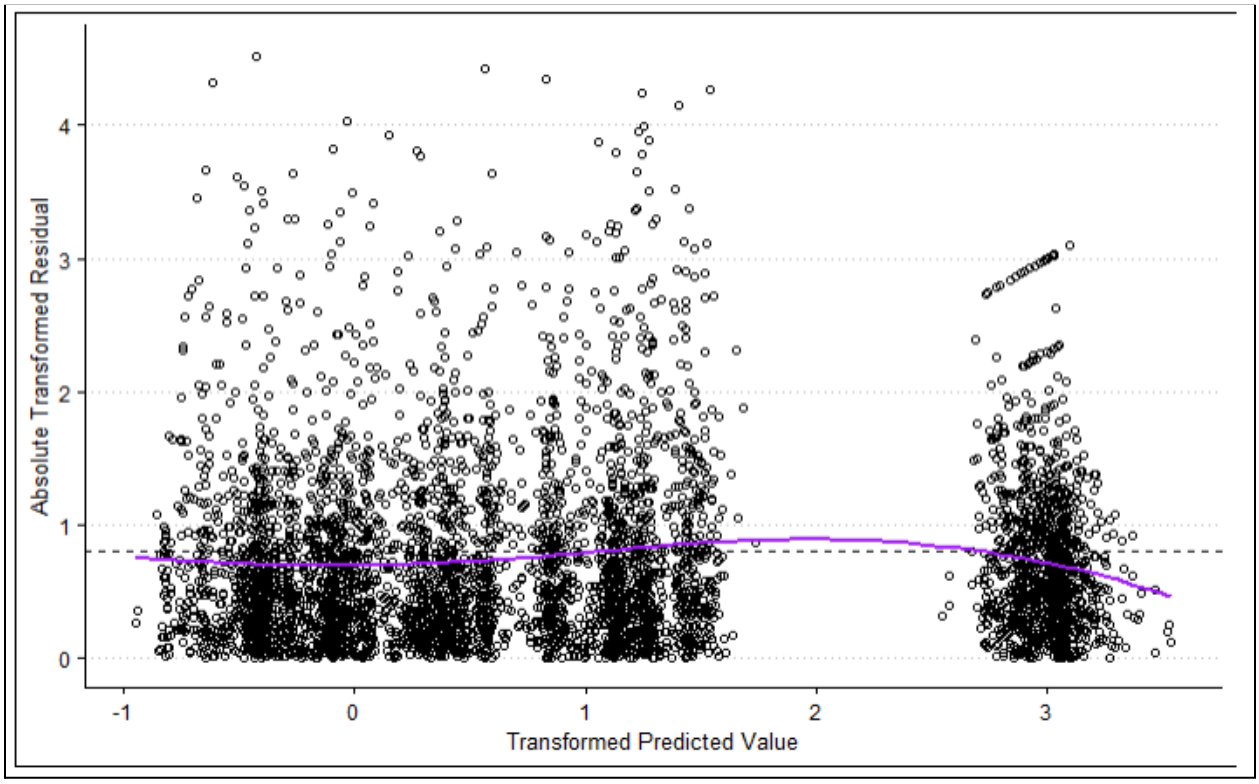
Next, we will analyze the constant variance assumption for the data. We transform time, and plot it against the transformed residuals. If correctly specified, the range of the transformed residuals should be constant over transformed time.



The scatterplot suggests that the points seem to fluctuate around 0, and we can see that the smooth line follows 0 almost perfectly through transformed time. This is indicative of the adequacy of the constant variance assumption in the data and solidifies our belief that a quadratic term is needed in our model.

Absolute Transformed Residuals ~ Transformed Predicted Values

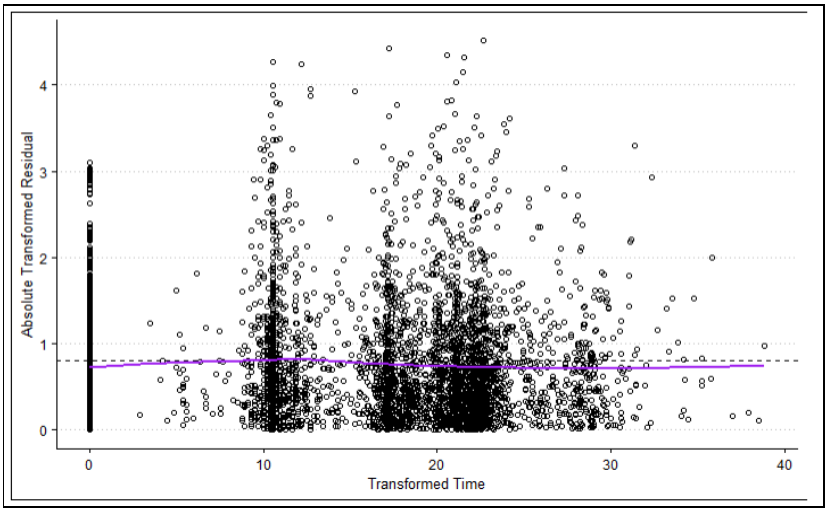
We plot the absolute transformed residuals vs the transformed predicted values to check the constant variance assumption for our chosen model. If the variance is adequate, no systematic trend will be visible on the graph. If assumed to be normally distributed (with mean 0 and variance 1), the fitted curve should be centered at approximately 0.8.



As we can see from the output, the points fluctuate around 0.8 quite well. With no systematic departures from 0.8, we can conclude that the residuals in our model follow a normal distribution with mean 0 and variance 1.

Absolute Transformed Residuals ~ Transformed Time

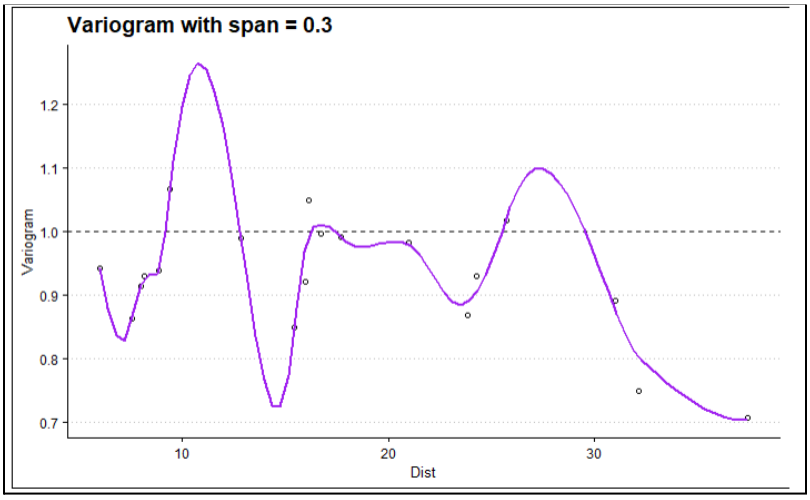
Similarly, we plot absolute transformed residuals against transformed time to double-check our conclusions from the previous plot.



Again, we can see our points fluctuate around 0.8 well and the smoothed line is also approximately 0.8. This solidifies our conclusion from the previous graphs that the variance assumption is met and that the residuals are approximately normal.

Semi-Variogram

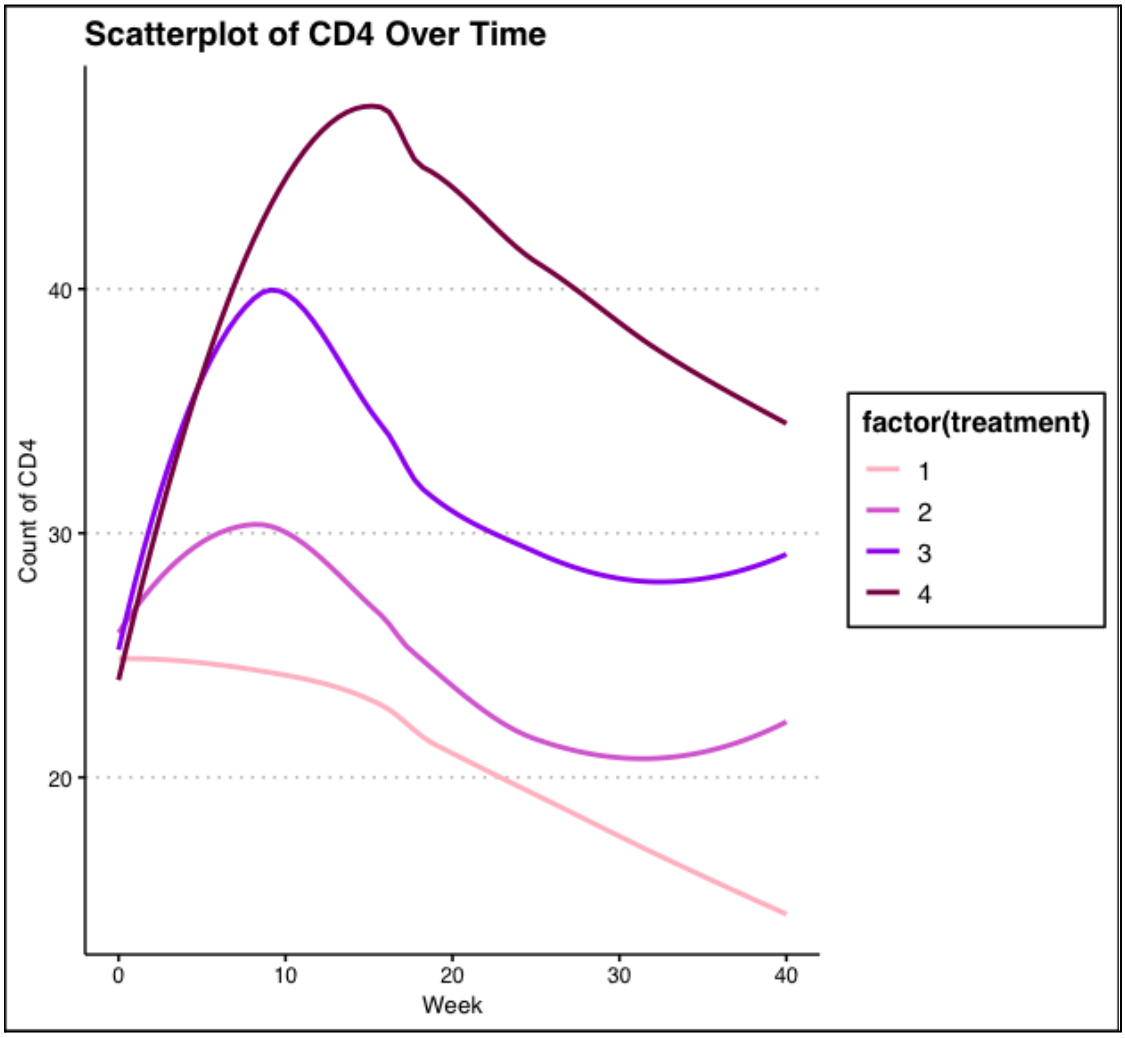
We will use the semi-variogram to assess the adequacy of the covariance in our selected model. If we have chosen the correctly specified model, the observation should fluctuate around the horizontal line centered at 1.



The variogram fluctuates around 1 randomly, indicating that covariance (and variance and correlation) is adequate for the model.

In summary, the residual analysis supports our specified model. There are no systematic errors in our model or changes needed.

GLME MODEL



To preface, we were unable to get the model to converge when including the main effect of gender, in addition to the interaction effects of age:treatment and gender:treatment. Additionally, note that we use CD4 count as our response variable (in contrast to log(CD4) in the LME model) through the following transformation: CD4 = round(exp(log(CD4)) - 1). As such, the GLME model looks like:

$$CD4 = \beta_0 + \beta_1 Age_i + \beta_2 Week_i + \beta_3 Week_i^2 + \beta_4 Week_i I(Trt = 2) + \beta_5 Week_i I(Trt = 3)$$

$$+ \beta_6 Week_i I(Trt = 4) + \beta_7 Week_i^2 I(Trt = 2) + \beta_8 Week_i^2 I(Trt = 3) + \beta_9 Week_i^2 I(Trt = 4)$$
$$+ b_{0i} + b_{1i} Week_i$$

The GLME summary is below:

```
Generalized linear mixed model fit by maximum likelihood
  (Adaptive Gauss-Hermite Quadrature, nAGQ = 0) [glmerMod]
 Family: poisson  ( log )
Formula:
count_cd4 ~ age + week + week_sq + week:treatment + week_sq:treatment +
    (1 + week | id)
   Data: aids

     AIC      BIC   logLik deviance df.resid
 52619.4  52704.2 -26296.7  52593.4     5023

Scaled residuals:
     Min       1Q   Median       3Q      Max
-10.0319  -1.0094  -0.0888   0.8061  18.3662

Random effects:
 Groups Name        Variance  Std.Dev. Corr
 id     (Intercept) 0.8683465 0.93185
        week        0.0009395 0.03065  -0.15
Number of obs: 5036, groups:  id, 1309

Fixed effects:
                    Estimate Std. Error z value Pr(>|z|)
(Intercept)         2.546e+00  1.228e-01  20.725  < 2e-16 ***
age                 9.890e-03  3.174e-03   3.115  0.00184 **
week                4.904e-03  2.521e-03   1.945  0.05178 .
week_sq            -7.753e-04  5.394e-05 -14.373  < 2e-16 ***
week:treatment2     5.743e-03  3.484e-03   1.648  0.09929 .
week:treatment3     2.714e-02  3.423e-03   7.929  2.2e-15 ***
week:treatment4     4.627e-02  3.364e-03  13.757  < 2e-16 ***
week_sq:treatment2 -8.539e-05  7.222e-05  -1.182  0.23704
week_sq:treatment3 -7.194e-04  6.966e-05 -10.326  < 2e-16 ***
week_sq:treatment4 -8.959e-04  6.719e-05 -13.334  < 2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

We wish to test the two hypotheses $H_0: \beta_4 = \beta_5 = \beta_6 = 0$ and $H_0: \beta_7 = \beta_8 = \beta_9 = 0$. The former tests whether different treatments have differing effects over time. The latter tests whether the rate of change of the treatments change over time. We can use a Wald Test on both hypotheses. For the former, we find a test statistic = 121.3127 and a p-value = 4.024577e-26 < 0.05 = alpha. We reject the null and conclude that there is sufficient evidence for the alternative. The treatments have differing effects over time. For the latter, we find a test statistic = 593.125 and a p-value = 3.11733e-128 < 0.05 = alpha. We reject the null and conclude that there is sufficient evidence for the alternative. The rates of change of treatments differ over time.

Individually, we can test the hypotheses $H_0: \beta_i = 0$ and $H_A: \beta_i \neq 0$ for i = 4, 5, 6. As the p-values equal 0.09, 2.2e-15, and 2.2e-16, we fail to reject the null for β_4, however reject the null for β_5 and β_6, respectively at $\alpha = 0.05$. We conclude that the interaction between Treatment 2 and week is not statistically significant, however the interaction between Treatment 3 and week in addition to Treatment 4 and week is statistically significant. Treatments 3 and 4 have statistically non zero effects on CD4 count over time.

Predictions/Comparisons of GLME Model

The model predicts that:

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 2 (Zidovudine plus 2.25mg of Zalcitabine), we expect a change in CD4 of $\beta_4 Week_i + \beta_7 Week_i^2$. For a 35-year old male at week 10, we'd expect a change in CD4 of 0.049.

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 3 (Zidovudine plus 400mg of Didanosine), we expect a change in CD4 of $\beta_5 Week_i + \beta_8 Week_i^2$. For a 35-year old male at week 10, we'd expect a change in CD4 of 0.199.

Going from Treatment 1 (Zidovudine alternating monthly with 400mg Didanosine) to Treatment 4 (Zidovudine plus 2.400mg of Didanosine plus 400mg of Nevirapine), we expect a change in log(CD4) of $\beta_6 Week_i + \beta_9 Week_i^2$. For a 35-year old male at week 10, we'd expect a change in CD4 of 0.37311.

We can also compare our model with the observed CD4 values. We choose subjects with IDs 2 and 149.

ID	**Week**	**Fitted**	**Observed**	**Fitted - Observed**
2 (Trt = 4, 47.84 y.o. male)	0	28.10	20	8.10
	8.00	39.26	48	-8.74
	16.00	44.29	52	-7.71
	23.00	41.30	36	5.3
	30.71	31.63	27	4.63
	39.00	19.03	21	-1.97
149 (Trt = 3, 28.44 y.o female)	0	14.26	16	-1.74
	8.00	16.11	12	4.11
	15.86	15.08	18	-2.92
	25.57	10.76	10	0.76

CONCLUSION

Both our chosen Linear Mixed Effects model and our General Linear Mixed Effects model provide useful information in interpreting the effect of the treatment type over time. In the LME model, we predicted the response, log(CD4), over time using the main effects of Age, Gender, Week and Week^2. We found that going from treatment 1 (reference) to treatment 3, and from treatment 1 (reference) to treatment 4 provided an increase in log(CD4) counts, indicating that the treatments had a significant positive effect.

Using the General Linear Mixed Effects Model, we conclude the treatments have differing effects in CD4 over time and the rates of change of CD4 also differ over time. Furthermore, we also came to the conclusion that the interaction term between week and treatments 3 and 4 individually are statistically significant, meaning that holding everything else constant, treatments 3 and 4 have a significant difference to the reference group (treatment 1) in the change of CD4 over time.

AIDS patients with advanced immunosuppression hoping to increase their CD4 count can have the assurance that the daily regimen of zidovudine plus 400mg of didanosine or a daily regimen if zidovudine plus 400mg of nevirapine, namely treatments 3 and 4, is predicted to have a net positive effect on their CD4 count.